

EXHIBIT 2

Perineal Use of Talc and Risk of Ovarian Cancer

Daniel Krewski, PhD, MHA
Professor and Director
McLaughlin Centre for
Population Health Risk Assessment

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Université d'Ottawa | University of Ottawa



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Ovarian Cancer

- Occurs at low rates among young women
- Increases with age
- Varies by ethnicity
- Average age at diagnosis in the US: 63 years
- Annual incidence rate: 12.7/100,000 (2005 – 2009)
- Majority of cases are diagnosed at an advanced stage, with 61% having distant metastases at the time of diagnosis

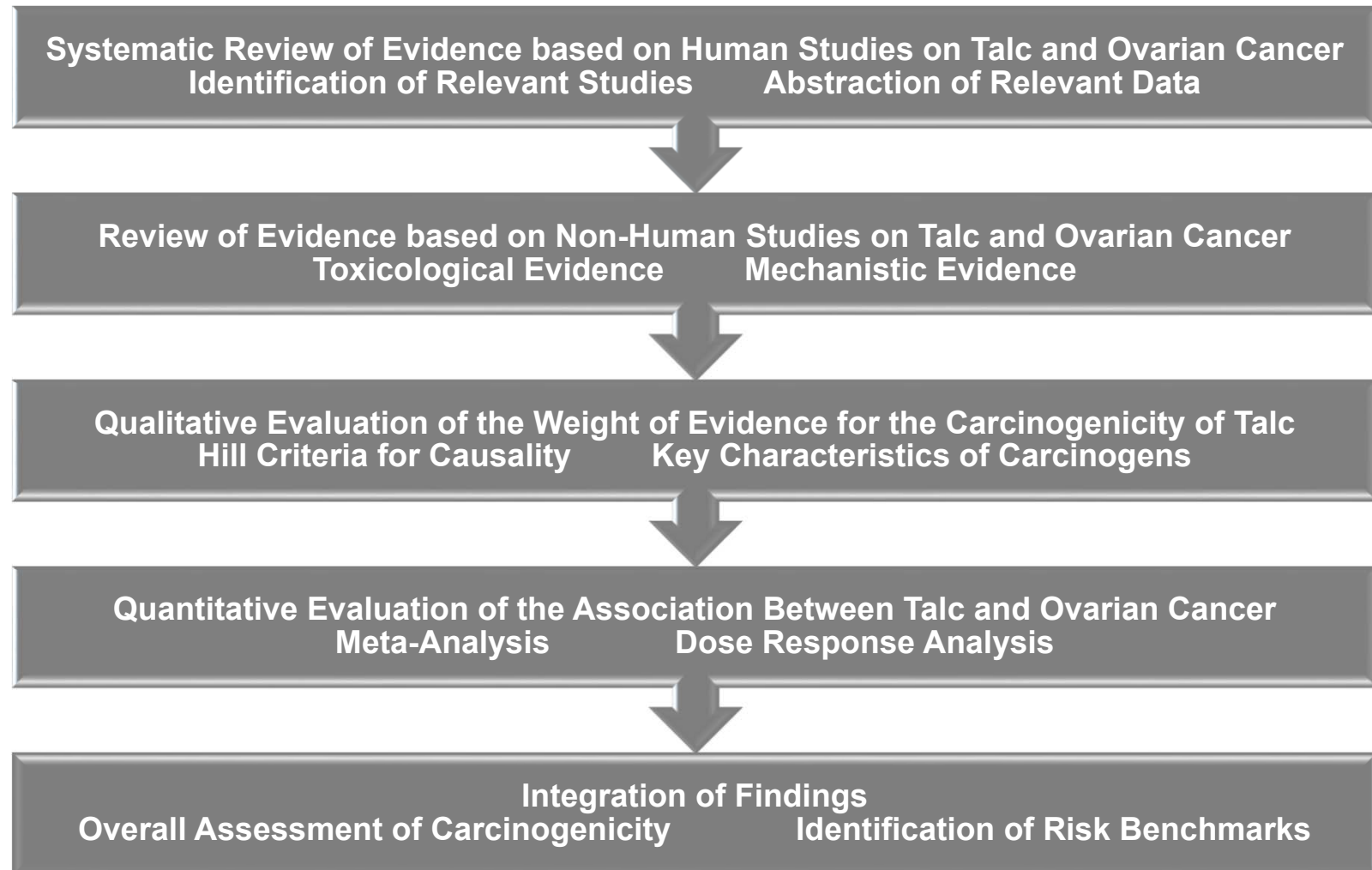
Previous Research

- Four decades of research on the association between talc and ovarian cancer in North America, Europe and Asia
- Epidemiological studies are somewhat inconsistent, with notable differences in exposure assessment and characterization of dose-response

Research Question

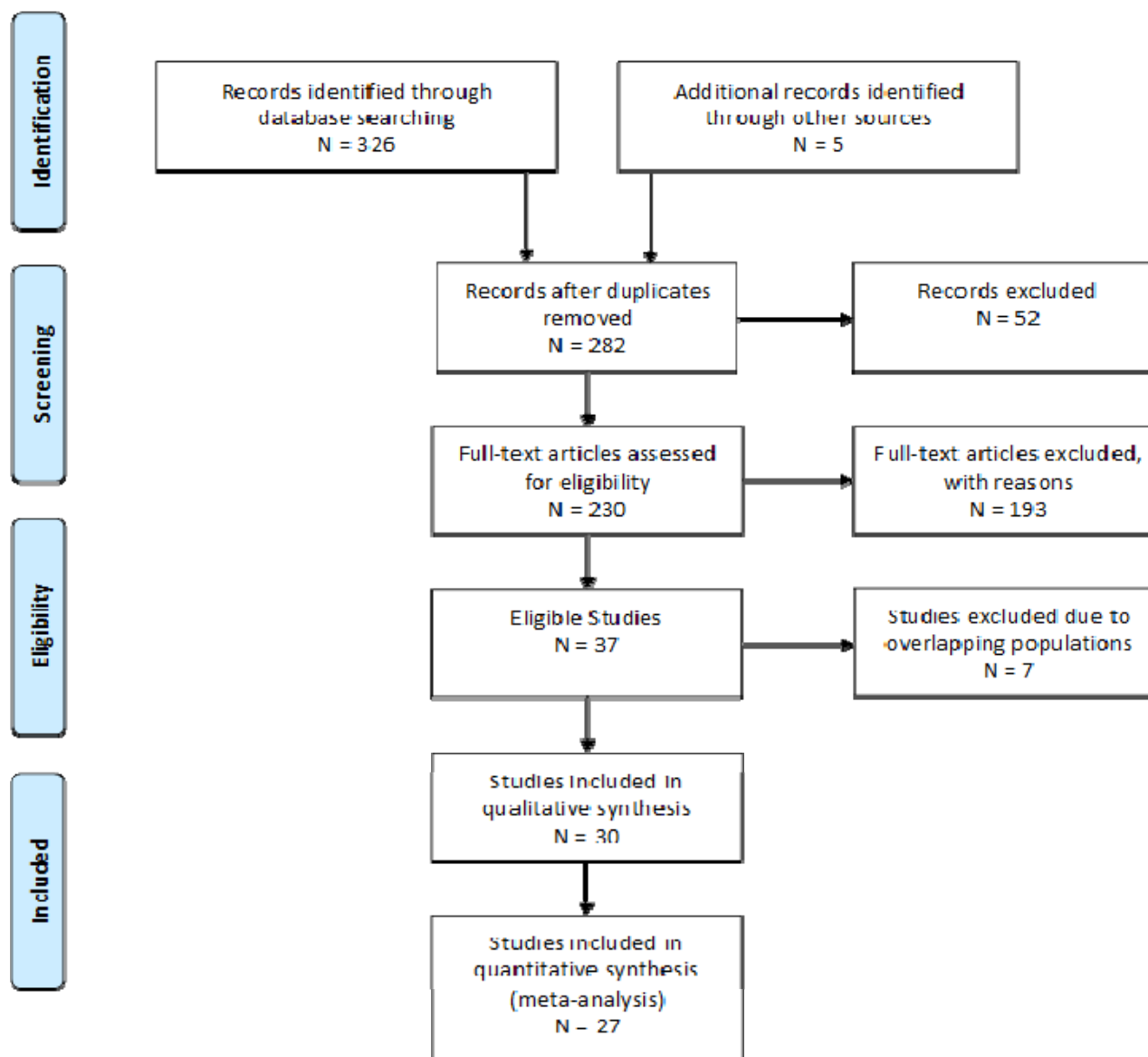
To investigate the association between the perineal use of talcum powder and the risk of ovarian cancer, using all available evidence from peer-reviewed human epidemiological data, as well as additional in-vitro or in-vivo studies.

Methodological Approach



Systematic Review

PRISMA Diagram



Qualitative Aspects of Current Review

- **Geography:** USA (n=21), Europe (n=4), Canada (n=2), Australia (n=2) and China (n=1)
- **Publication Time:** 40% (n=12) in the last decade, with the remaining studies (n=18) conducted between 1982 and 2006
- **Purpose:** Several studies analyzed data from populations initially recruited for other purposes, such as the Nurses' Health Study (NHS) and Women's Health Initiative (WHI) in the US
- **Number of studied women:** 46 – 2,204

Conclusions of Previous Studies

- Fifteen of 30 studies concluded a positive association
- Five studies reported the possibility of an association
- Nine studies concluded an absence of an association
- One study did not present a concluding statement

Weight of Evidence

(application of Bradford Hill Criteria)

1. Strength of Association

- Of the 30 epidemiological studies, six reported statistically significant positive associations, with risk estimates (RR or OR) of 1.5 or greater
- None of the cohort studies (n=3) found a statistically significant association

2. Consistency

- Fifteen of 30 studies reported significant positive associations:
 - over four decades;
 - in different ethnicities;
 - across several countries, and several US states;
 - in case-control studies, but not cohort, studies.

3. Specificity

- Perineal talc exposure is specifically associated with cancer of the ovary and not other organs or tissues
- Findings suggest that the association may be stronger for serous ovarian cancer compared to other histologic types

4. Temporality

- **Case-control studies** reporting positive outcome, the participants recalled that exposure to talc preceded the reported outcome.
- **Cohort studies** (reporting lack of positive association), it is not known whether the follow up period was adequate to detect a potential association between perineal talc exposure and ovarian cancer

5. Biological Gradient

- About half of the epidemiological studies assessed only one level of talc exposure (ever vs never usage).
- Of those studies reporting a positive association, 6 studies found significant increasing dose response trends.

6. Biological Plausibility

- Particles of talc appear to migrate into the pelvis and ovarian tissue causing irritation and inflammation (the presence of talc in the ovaries has been documented)
- The specific mechanism(s) and cascade of molecular events by which talc might cause ovarian cancer have not yet been elucidated
- Chronic inflammatory response and alteration in local immunogenicity are possible mechanisms of action of talc as a risk factor for ovarian cancer

7. Coherence

- Results from talc epidemiology studies are coherent with the current knowledge on risk factors for ovarian cancer.
- Factors/physiological states associated with greater frequency and duration of ovulation appear to be associated with increased risk of ovarian cancer.
- Multiple case-control studies reported lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation and suppressed ovulation.

8. Experimental Evidence

- Lack of long-term animal studies on talc carcinogenicity following perineal exposure.
- The rodent cancer bioassay for talc conducted by the National Toxicology Program (1993) was only by the inhalation route
- Rodent models may be of limited relevance because of ovulation occurring only or mainly during the breeding season, the rarity of ovarian epithelial tumors in these animals, and ovaries being variously enclosed in an ovarian bursa.

9. Analogy

- Talc and asbestos are both silicate minerals.
- Talc has been variably contaminated with asbestos (tremolite and anthophyllite). Until 1976, talcum powders were only required to contain at least 90% mineral talc
- Pleural and peritoneal mesotheliomas caused by asbestos are histologically similar to epithelial ovarian cancer associated with talc
- In animal models, asbestos induces ovarian epithelial hyperplasia similar to early epithelial tumors reported in women with prior exposure to talc

Meta-Analysis

Meta-analyses Conducted

Primary analysis

- *Perineal talc use (ever vs. never)*

16 Subgroup Analyses

- *Duration and frequency of talc exposure*
- *Tumor histology, tumor behavior*
- *Study design, type of study controls*
- *NOS quality score and the publication year*
- *Effect of the menopausal state, hormone use, pelvic surgery*

Results of Primary Meta-analysis

- Perineal/genital talc is associated with a significant increased risk of epithelial ovarian cancer:

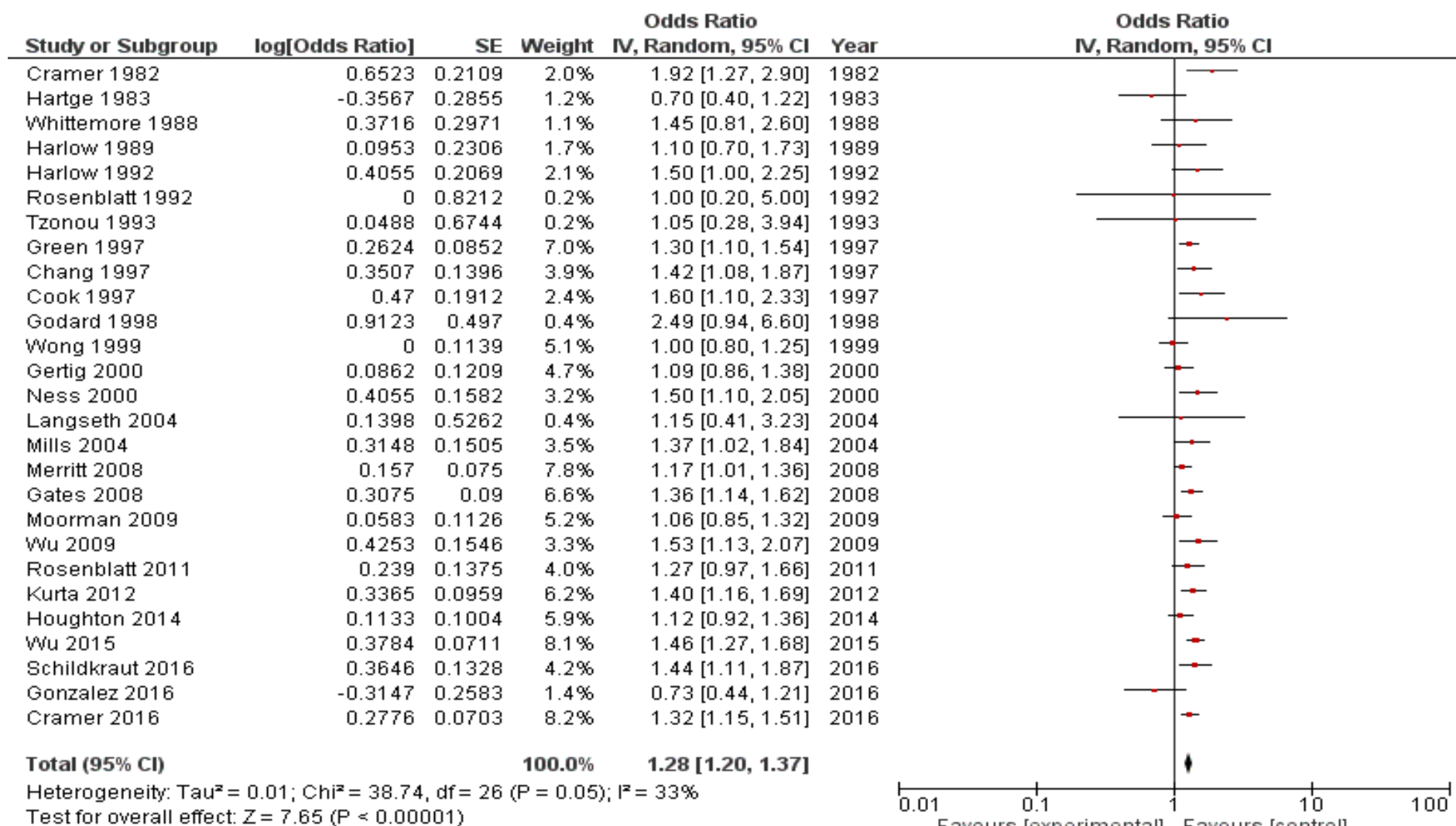
OR: 1.28 [1.20, 1.37]

P-heterogeneity= 0.05

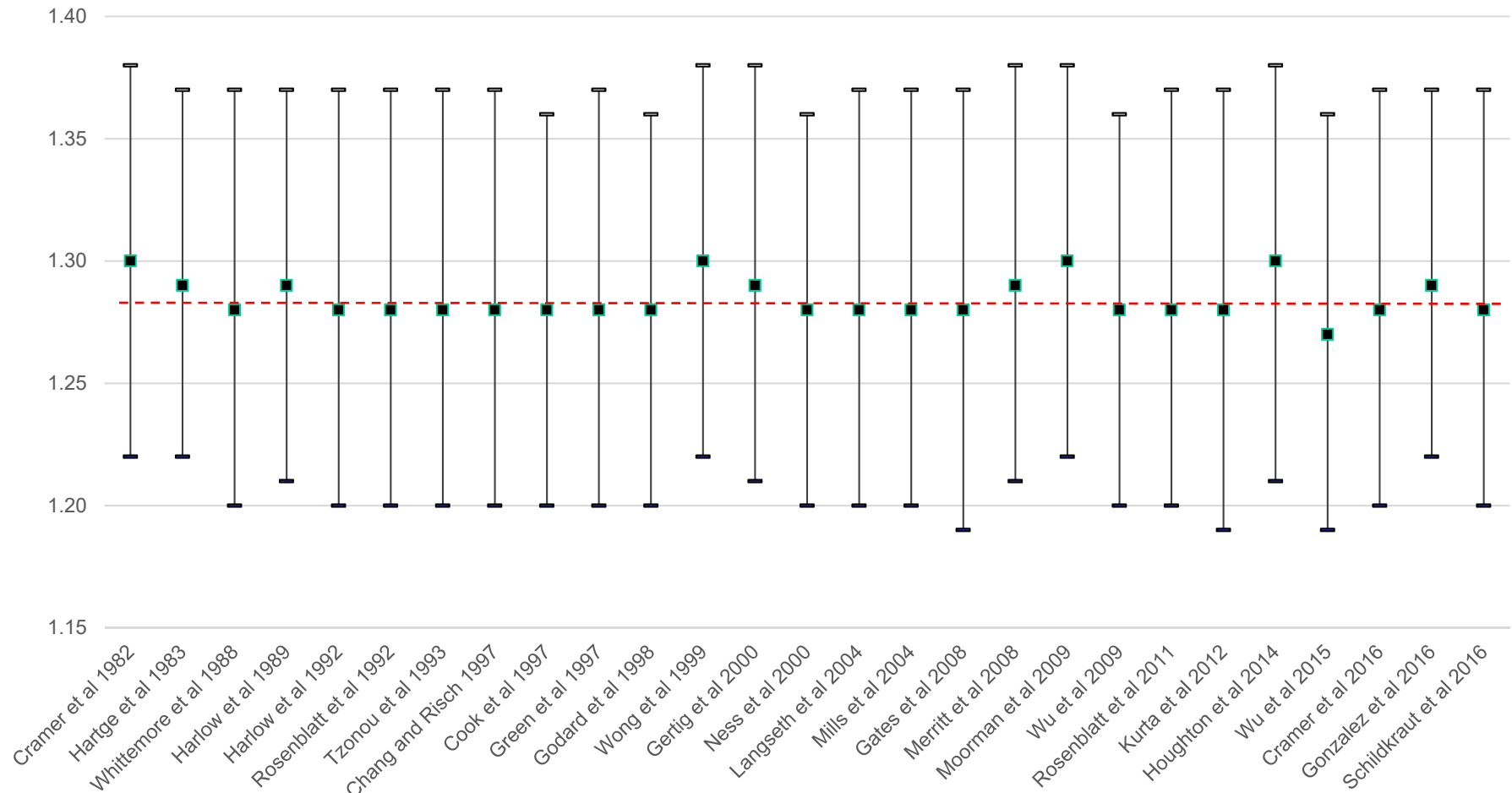
$I_2 = 33\%$

Results of Primary Meta-analysis

(ever vs. never use of talc)



Influence Analysis



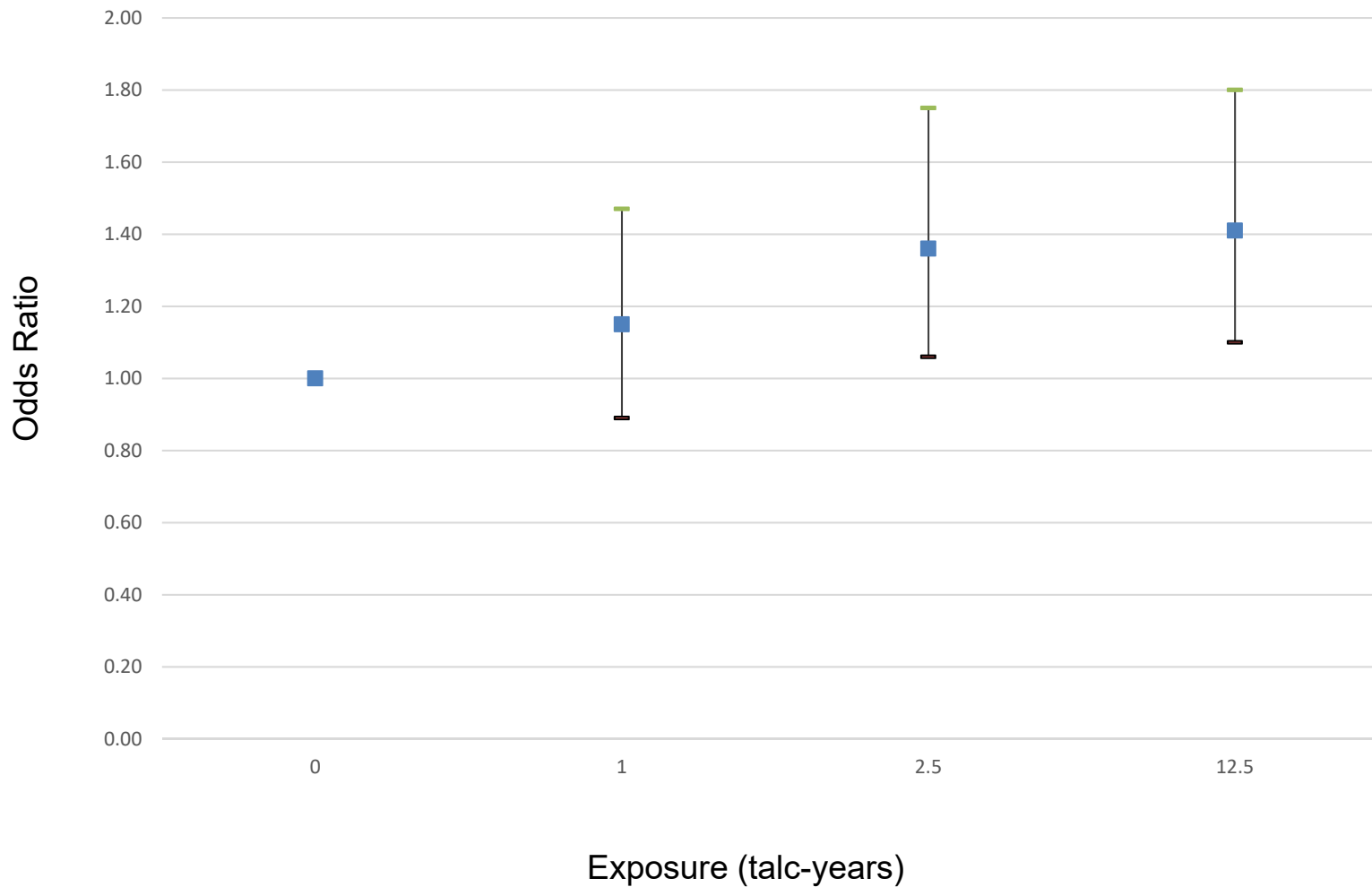
--- Overall pooled odds ratio

Results of Subgroup Analyses

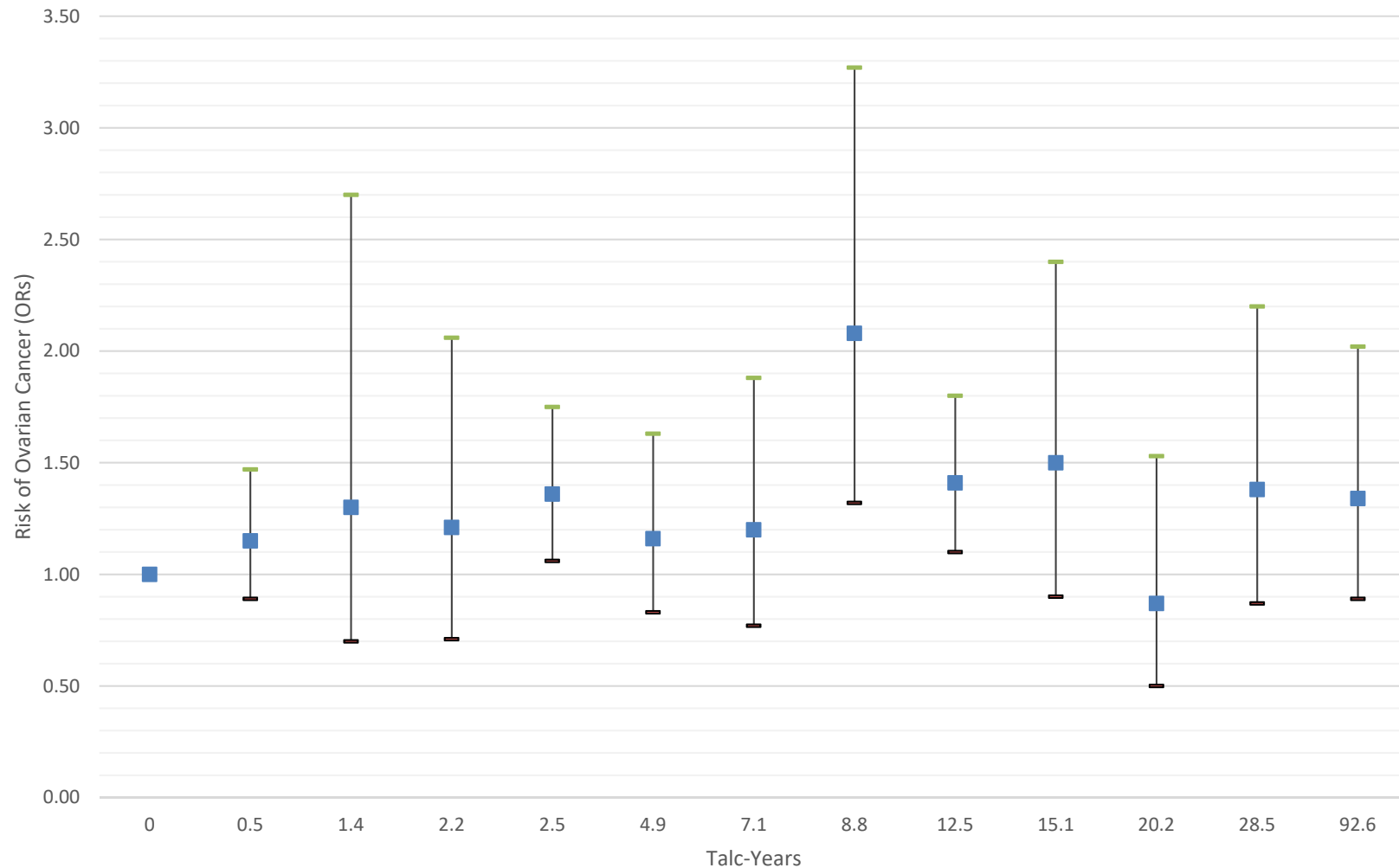
- Elevated risk more pronounced in:
 - *Hispanics and Whites*
 - *Women applying talc to underwear*
 - *Pre-menopausal women and post-menopausal women receiving hormonal therapy*
 - *Serous and endometrioid types of epithelial ovarian cancer*
- Negative association noted with tubal ligation

Exposure-response Analysis

Exposure-response Data from Cramer et al. (2016)



Exposure-response Data from Multiple Studies



Conclusion

Cancer Classification

Review	Conclusion	Criteria for Classification
IARC (2010)	Possibly carcinogenic to humans (Group 2B)	Group 2B: The agent (mixture) is possibly carcinogenic to humans. “. . . the Working Group concluded that the epidemiological studies taken together provide limited evidence of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.”
This Review	Possibly Carcinogenic to Humans (Health Canada Group IIIA)	Group IIIA: Possibly Carcinogenic to Humans. Data from epidemiological studies indicate an association between exposure and human cancer, but alternative explanations such as chance, bias or confounding cannot be excluded.

Risk Estimates

Review	No. of Studies			No. of Participants		Risk of Ovarian Cancer [95% CI]
	Cohort	Case-Control	Total	Cases	Controls	
Huncharek et al. (2003)	1	15	16	5,260	6,733	1.33 [1.16, 1.45]
Langseth et al. (2008)	1	20	21	NR	NR	1.35 [1.26, 1.46]
Terry et al. (2013)	0	8	8	8,525	9,859	1.35 [1.26, 1.46]
Berge et al. (2017)	3	24	27	15,019	18,851	1.22 [1.13, 1.30]
Current Review	3	24	27	16,352	19,808	1.28 [1.20, 1.37]

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Contributors

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